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Synthesis, antibacterial, and molecular docking of some new tetrazole, oxazepine, and thiazolidine derivatives contacting with an aromatic nucleus

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ABSTRACT

The study aims to synthesize heterocyclic derivatives (five and seven-membered) rings linked to an aromatic nucleus containing nitrogen, oxygen, and sulfur in its structure. Schiff's bases were used for the synthesis processes. 2-bromo-6-methylaniline was used as an aromatic amine to react with aromatic aldehydes (furfural and salicyldehyde) to prepare Schiff bases (A and B) using ethanol as a solvent and glacial acetic acid as a catalyst, Schiff bases (A and B) were reacted with sodium azide using 1,4-dioxane as a solvent to obtain tetrazole derivatives (A1 and B1). Schiff bases (A and B) were also reacted with phthalic anhydride, and dry benzene was used as a catalyst to obtain oxazepine derivatives (A2 and B2). Schiff bases (A and B) were also reacted with thioglycolic acid, and 1,4-dioxane was used as a solvent to obtain thiazolidine derivatives (A3 and B3). All reactions were monitored using the thin-layer chromatography technique (TLC). The physical properties of the prepared derivatives were obtained, and they were studied spectroscopically using FT-IR, ^{1}H-NMR, and ^{13}C-NMR techniques. The biological activity against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus* bacteria was studied. The effect of the prepared derivatives was theoretically studied against the protein responsible for prostate cancer (1E3G) using Molecular Docking software.

1. Introduction

The composition of heterocyclic compounds varies depending on the type of atoms associated with them and the atoms that make up their structure [1,2], but they often contain at least one heteroatom other than the carbon atom, such as nitrogen, oxygen, and sulfur atoms [3,4]. The most common heterocyclic compounds are five-membered or six-membered ring compounds. These compounds can also be divided into saturated, unsaturated, or aromatic [5-7]. The difference in the composition of heterocyclic compounds makes them compounds with a wide range of use in various fields of life [8-11], such as the pharmaceutical industry [12], pesticides [13], the plastics industry[14], cosmetics, and other industries[15]. Schiff bases resulting from the reaction of primary (aromatic) amines with aldehydes or ketones are considered one of the best intermediates through which various heterocyclic compounds can be obtained, such as tetrazole, oxazepine, thiazolidine, and other heterocyclic compounds[16-20]. Tetrazole is a five-membered ring form containing four nitrogen atoms and one carbon atom [21]; it is one of the heterocyclic compounds widely used in pharmaceutical chemistry[22]. Oxazepine is an unsaturated (non-aromatic) seven-member ring compound that contains two different atoms in its structure (nitrogen and oxygen). It is used less frequently in pharmaceutical industries with biological activity [23-25]. The thiazolidine ring consists of nitrogen and sulfur atoms. Thiazolidine compounds are known to exhibit interesting and pharmacological activity. Specifically, they are applied as an antiseizure, fungicidal and

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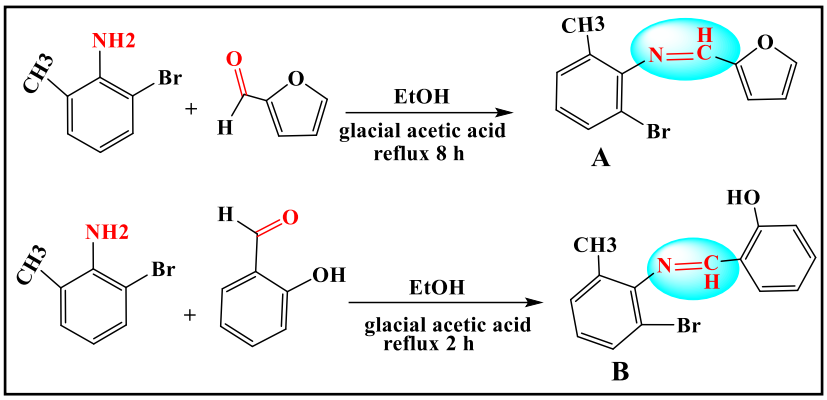


Scheme 1. Preparation of Schiff bases

antibacterial [26-28]. Prostate cancer is one of the most common types of cancer among men all over the world [29].The development and differentiation of the prostate depend on the androgen hormone dihydrotestosterone (DHT), which is extracted from testosterone in the prostate [30]. Any genetic defect in the androgen receptors leads to many pathological conditions, the most important of which is prostate cancer and Androgen Insensitivity Syndrome (AIS)[31]. Inhibiting androgen biosynthesis enzymes prevents the production of androgens, which has been proven to be an effective treatment for prostate cancer. This is done by inhibiting androgen receptors, including the 1E3G protein[32].

2. Chemicals and materials

All chemicals and solvents were obtained from Fluka, Merck, and Sigma Aldrich. Stuart, UK capillary melting point apparatus was used to measure the melting points. FT-IR Spectra (400 - 4000 cm-1) with the KBr disk recorded on a BRUKER -8400S Fourier transform..^{13}C-NMR and ^{1}HNMR recorded on Fourier transformation BRUKER Spectrometer operating at (400MHz) with (DMSO-*d6*) with TMS as an internal standard.

3. Experimental

3-1- General procedure of Schiff bases A- (Z)-N-(2-bromo-6-methylphenyl)-1-(furan-2-yl) methanimine and B-(E)-2-(((2-bromo-6-methylphenyl)imino) methyl) phenol

Two Schiff bases(**A** and **B**) were prepared by dissolving specific quantities of (2-Bromo-6-methylaniline) with aldehyde compounds (furfural and salicylaldehyde) in absolute ethanol adding to the mixture 3drops of glacial acetic acid and the escalation process for the prepared mixture at a temperature of 79°C TLC monitored the process of the reaction through the use of the mobile phase (methanol-benzene) at a ratio of (1:4) (Scheme 1).

3-2- Synthesis of tetrazole derivatives A1- 1-(2-bromo-6-methylphenyl)-5-(furan-2-yl)-2,5-dihydro-1H-tetrazole and B1- 2-(1-(2-bromo-6-methylphenyl)-2,5-dihydro-1H-tetrazol-5-yl)phenol

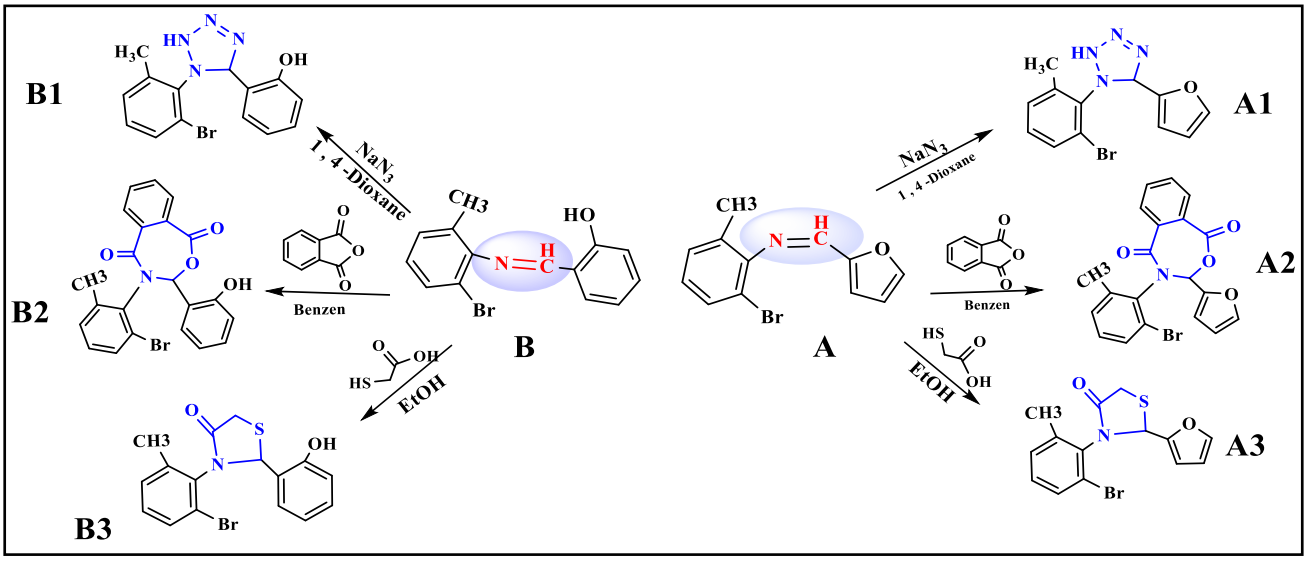
1 mmol of Schiff bases (264 mg **A** and 219 mg **B**) were dissolved in (20 ml) of 1,4 dioxane and mixed with (10 mmol) of sodium azide. These mixtures were refluxed for (13 and 18 h) respectively at (55 ^{0}C). The crystals formed were filtered, dried, and recrystallized.

3-3- Synthesis of oxazepine derivatives A2- 4-(2-bromo-6-methylphenyl)-3-(furan-2-yl)-3,4dihydrobenzo[1,3] oxazepine-1,5-dione and B2-4-(2-bromo-6-methyl phenyl)-3-(2-hydroxyphenyl)-3,4-dihydrobenzo[1,3] oxazepine-1,5-dione

1 mmol of Schiff bases (264 mg **A** and 219 mg **B**) were dissolved in (25 ml) of dry benzene and mixed with one mmole (148 mg) of phthalic anhydride . The mixture was refluxed for (18 and 21 h) respectively at (70 ^{0}C) and then cooled. The crystals formed were filetred, dried and recrystallized from ethanol.

3-4- Synthesis of thiazolidine derivatives A3-3-(2-bromo-6-methylphenyl)-2-(furan-2-yl)Thiazolidine-4-one and B3-3-(2-bromo-6-methylphenyl)-2-(2-hydroxy phenyl) thiazolidin-4-one

Thioglycolic acid (1 mmole) in 1, 4- Dioxane (20 mL) was added to (1 mmole) of Schiff bases (264 mg **A** and 219 mg **B**). Then (500 mg) of anhydrous zinc chloride was added to the mixture with stirring and refluxed for (16 hours). The reaction mixture was cooled and kept for (32 and 30 h) respectively. Crystals were formed, filtered, dried, and recrystallized from ethanol, see Scheme 2. and Table.1



Scheme 2. Preparation compounds

Table 1: Physical properties of compounds

Compound	M.F	Color	M.Wt.	m.p °C	Rf.	Yield %
A	$C_{12}H_{10}BrNO$	Brown	264	166-170	0.58	81
B	$C_{14}H_{12}BrNO$	Yellow	290	188-190	0.53	85
A1	$C_{12}H_{11}BrN_4O$	Brown	307	155-157	0.51	66
B1	$C_{14}H_{13}BrN_4O$	Orange	333	178-180	0.44	68
A2	$C_{20}H_{14}BrNO_4$	Brown	412	199-201	0.48	66
B2	$C_{22}H_{16}BrNO_4$	Yellow	438	180-182	0.49	76
A3	$C_{14}H_{12}BrNO_2S$	Dark brown	338	185-187	0.50	77
B3	$C_{16}H_{14}BrNO_2S$	Brown	364	169-171	0.50	62

4. Results and discussion

4-1-Characterization of Schiff bases (**A**& **B**)

FT-IR data (cm^{-1}): 3023,3054 ($C\text{-}H_{aromatic}$), 1624, 1614(CH=N), 1194,1176(C-N), 1233 (C-O), 644(C-Br). ^{1}H-NMR δ : 8.64,8.88(CH=N), 7.10-7.43, 7.03-7.70($H_{aromatic}$),6.96(OH),2.31(CH_3).^{13}C-NMR δ: 164.02 (OH), 160.77,160.08(CH=N), 146.82,146.82 (C-N),117.06-134.9,119.67-134.95.82($C=C_{aromatic}$), 154.41 (=C-O), 117.06(C-Br), 18.99,17.93(CH_3).

4-2-Characterization of tetrazole derivatives (**A1** & **B1**)

FT-IR data (cm^{-1}): 3387, 3410(N-H) ,1490, 1477(C=C) , 1302,1307 (N-N=N), 1181,11765 ($C\text{-}N_{stretching}$) ,1205(C-O). ^{1}H-NMR δ : 8.47,8.87 (tetrazole-H), 7.68(OH), 7.05-7.44, 7.25-7.66 (aromatic H), 7.05-7.44(furan H), 2.30,226 (CH_3). ^{13}C-NMR δ:153.08,163.75(=C-O) , 148.31,146.90 (=C-N), 117.06-134.95, 119.95-136.47($C=C_{aromatic}$), 17.88, 17.91(CH_3).

4-3-Characterization of oxazepine derivatives (**A2** & **B2**)

FT-IR data (cm^{-1}):3415(OH), 3033, 3029($C\text{-}H_{aromatic}$), 2910($C\text{-}H_{aliphatic}$) 1707,1704 (C=O), 1486,1528(C=C), 1077,1074(C-N) . ^{1}H-NMR δ : 8.81,8.83 (O-CH-N), 7.10-7.99, 6.99-7.87(aromatic H), 6.50-6.99 (furan H). ^{13}C-NMR δ : 168.14,169.09 (C=O), 139.20-139.23(=C-N),128.06-136.24,128.10-136.26($C=C_{aromatic}$), 124.06,124.06 (=C-Br), 17.97, 17.66 (CH_3).

4-4-Characterization thiazolidine derivatives (**A3** & **B3**)

FT-IR data (cm^{-1}): 3395(O-H), 2960,2981(CH_2-S), 1730,1723(C=O), 1485(C=C), 1180,1170(C-S), 611,704 (C-Br). ^{1}H-NMR δ : 8.63(OH), 7.36-7.62, 6.74-7.42(aromatic-H),7.17-7.33(furan-H), 7.01,6.60 (CH-N), 3.71, 3.88(CH_2-S), 2.22, 2.25(CH_3). ^{13}C-NMR δ : 169.94, 169.55(C=O), 150.41($C\text{-}O_{furan}$), 135.97, 154.41(=C-N), 119.50-147.76, 119.66-146.86 ($C=C_{aromatic}$), 41.19,40.66(C-S) ,18.99(CH_3).

4.5- Biological activity[33-36]

The biological effectiveness of all the derivatives that were prepared was tested. The test was conducted against two types of bacteria: Gram-negative (*Escherichia coli)* and Gram-positive (*Staphylococcus)*. The prepared bacteria were spread on the culture medium in Petri dishes using (loopful), and drilling was done using (cork-borer). Solutions of the derivatives were added to drilling using a Micropipette, the plates were incubated for 24 hours at 37°C, the inhibition zones were measured, and the results are shown in Table 2.

Table 2. The biological activity of the prepared compound

Comp.	*E. Coli* gram (-)		*Staphylococcus* gram (+)	
A	0.7	++	0.4	+
B	1.0	+++	0.7	+++
A1	0.8	+++	0.7	+++
B1	0.6	++	0.9	+++
A2	0.6	++	0.8	+++
B2	0.4	+	0.6	++
A3	0.5	++	0.3	+
B3	0.8	+++	0.9	+++
0.1 – 0.4 cm (+) , 0.5 – 0.7cm (++) , 0.8 – 1.0 cm(+++)				

4-6- Molecular docking study[37-39]

Molecular docking of the prepared derivatives into the active pocket of the IE3G target protein was performed using AutoDock 4.2.6. The crystallographic structure of the target protein was retrieved from the Protein Data Bank (www.rcsb.org). All structures were loaded to the discovery studio visualized, unwanted ligands, water, and H-atoms were removed, and other parameters were used. The 2D illustration of the docked complexes of the ligand-receptor was visualized by PyMol (www.pymol.org) and Discovery Studio 2021 client. The best docking scores were chosen for the MD simulator; the results shown in Table 3 and Figures 1 and 2

Table 3. Results of molecular docking of synthesized derivative

Compound	Lowest Binding Energy ΔG (kcal/mol)	Run
A	-7.19	1
B	-6.93	25
A1	-5.94	27
B1	-5.70	14
A2	-7.82	40
B2	-7.70	18
A3	-5.50	43
B3	-7.34	29

5- Conclusion

New heterocyclic derivatives were synthesized, which connected with an aromatic nucleus, excellent yields were obtained, TLC monitored the reactions' progress, and spectral analysis confirmed their structures. All the synthesized compounds were evaluated for their antibacterial activities. The results indicated that all the prepared derivatives have inhibitory activity against bacteria, but to varying extents. The derivatives **B**, **A1**, and **B3** are the most effective inhibitory activity against both types of bacteria. The results of the Molecular Docking study showed that the derivatives **A**, **A2**, and **B2** have more interactions with the active pocket of IE3G protein (androgen receptor), which is responsible for prostate cancer because these derivatives have the lowest binding energy with the protein units ΔG (kcal/mol).

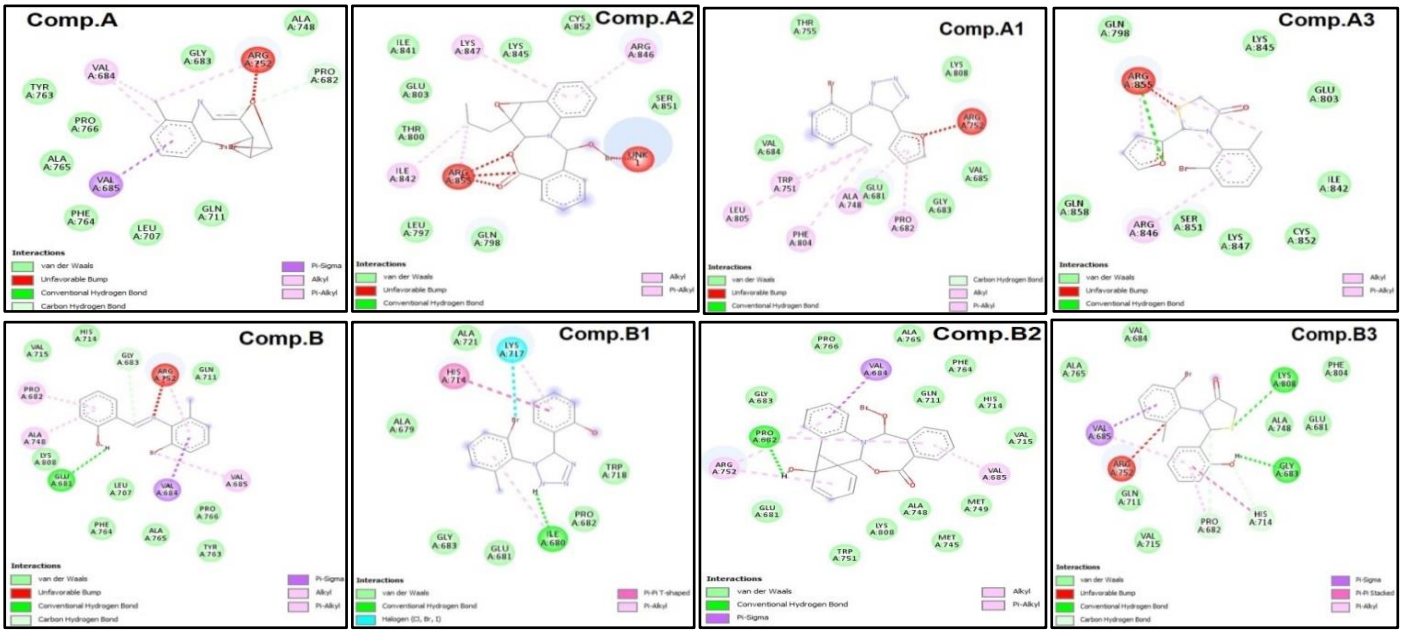


Fig. 1. 2D interaction diagrams between compounds and IE3G protein

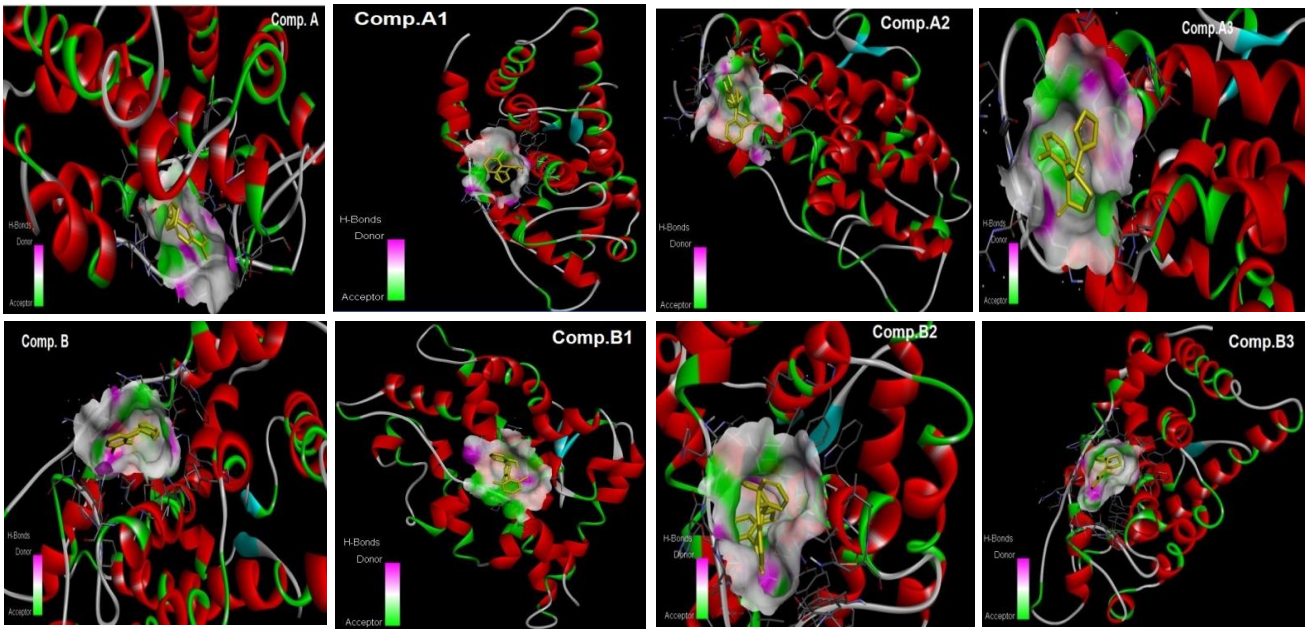


Fig. 2. 3D interaction diagrams between compounds and IE3G protein

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